L16 ANSWER 13 OF 13 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1999338865 MEDLINE
DOCUMENT NUMBER: 99338865 PubMed ID: 10410676
TITLE: Amyloid formation by mutant huntingtin: threshold, progressivity and recruitment of normal polyglutamine proteins.
AUTHOR: Huang C C; Faber P W; Persichetti F; Mittal V; Vonsattel J P; MacDonald M E; Gusella J F
CORPORATE SOURCE: Molecular Neurogenetics Unit, Massachusetts General Hospital, Charlestown 02129, USA.
CONTRACT NUMBER: MH/NS31862 (NIMH)
NS16367 (NINDS)
NS32765 (NINDS)
SOURCE: SOMATIC CELL AND MOLECULAR GENETICS, (1998 Jul) 24 (4) 217-33.
Journal code: 8403568. ISSN: 0740-7750.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 20020924
Entered Medline: 19990730

AB **Huntington**'s disease (HD) is caused by an expanded CAG trinucleotide repeat encoding a tract of consecutive glutamines near the amino terminus of huntingtin, a large protein of unknown function. It has been proposed that the expanded polyglutamine stretch confers a new property on huntingtin and thereby causes cell and region-specific neurodegeneration. Genotype-phenotype correlations predict that this novel property appears above a threshold length (approximately 38 glutamines), becomes progressively more evident with increasing polyglutamine length, is completely dominant over normal huntingtin and is not appreciably worsened by a double genetic dose in HD homozygotes. Recently, an amino terminal fragment of mutant huntingtin has been found to form self-initiated fibrillar aggregates in vitro. We have tested the capacity for aggregation to assess whether this property matches the criteria expected for a fundamental role in HD pathogenesis. We find that that in vitro aggregation displays a threshold and progressivity for polyglutamine length remarkably similar to the HD disease process. Moreover, the mutant huntingtin amino terminus is capable of recruiting into aggregates normal glutamine tract proteins, such as the amino terminal segments of both normal huntingtin and of TATA-binding protein (TBP). Our examination of in vivo aggregates from HD post-mortem brains indicates that they contain an amino terminal segment of huntingtin of between 179 and 595 residues. They also contain non-huntingtin protein, as evidenced by immunostaining for TBP. Interestingly, like the in vitro aggregates, aggregates from HD brain display **Congo red** staining with green birefringence characteristic of amyloid. Our data support the view that the expanded polyglutamine segment confers on huntingtin a new property that plays a determining role in HD pathogenesis and could be a target for treatment. Moreover, the new property might have its toxic consequences by interaction with one or more normal polyglutamine-containing proteins essential for the survival of target neurons.

L4 ANSWER 38 OF 55 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:887989 CAPLUS
DOCUMENT NUMBER: 123:276079
TITLE: Compositions and methods for advanced glycosylation endproduct-mediated modulation of amyloidosis
INVENTOR(S): Vitek, Michael P.; Cerami, Anthony; Bucala, Richard J.; Ulrich, Peter C.; Vlassara, Helen; Zhang, Xini
PATENT ASSIGNEE(S): Picower Institute for Medical Research, USA
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9520979	A1	19950810	WO 1995-US1380	19950202
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2182731	AA	19950810	CA 1995-2182731	19950202
AU 9518701	A1	19950821	AU 1995-18701	19950202
AU 692237	B2	19980604		
EP 802797	A1	19971029	EP 1995-910911	19950202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT				
JP 09511492	T2	19971118	JP 1995-520751	19950202
US 6410598	B1	20020625	US 1995-477364	19950607
US 5935927	A	19990810	US 1996-501127	19960810

PRIORITY APPLN. INFO.:
US 1994-191579 A 19940203
US 1994-311768 A 19940923
WO 1995-US1380 W 19950202
US 1995-457169 A2 19950601

OTHER SOURCE(S): MARPAT 123:276079

ANSWER 38 OF 55 CAPLUS COPYRIGHT 2003 ACS

AB The present invention relates generally to the nonenzymic glycosylation of amyloidogenic proteins and the consequent formation of advanced glycosylation endproducts (AGEs). It has been found that formation of AGE-amyloidogenic proteins can enhance amyloidosis. The invention further relates to compns. and methods for the prevention and treatment of amyloidosis assocd. with amyloid diseases, particularly **neurodegenerative** disease and Type II diabetes, and more particularly Alzheimer"s disease. In a specific example, aggregation of an amyloidogenic peptide, .beta.-AP, is enhanced by the glycosylation reaction of .beta.-AP to form AGE-.beta.-AP as defined herein. Accordingly, the invention extends to a method for modulating the in vivo aggregation of amyloid polypeptides and assocd. amyloidosis by controlling the formation and presence of AGE-amyloid polypeptide. A corresponding diagnostic utility comprises the measurement of the course and extent of amyloidosis by a measurement of the presence and amt. of AGEs and particularly, AGE-amyloid. An assay is included that may use the AGE-amyloid polypeptide of the present invention to identify disease states characterized by the presence of AGE-amyloid. Addnl., such an assay can be utilized to monitor therapy and thus adjust a dosage regimen for a given disease state characterized by the presence of AGE-amyloid. Prepn. of AGE-thioflavins is also described. Binding to amyloid of a thioflavin T-amadori product was demonstrated.

Entered Medline: 20000525

L4 ANSWER 18 OF 55 MEDLINE
ACCESSION NUMBER: 2001087352 MEDLINE
DOCUMENT NUMBER: 20493368 PubMed ID: 11036200
TITLE: Amyloid-like inclusions in **Huntington**'s disease.
AUTHOR: McGowan D P; van Roon-Mom W; Holloway H; Bates G P; Mangiarini L; Cooper G J; Faull R L; Snell R G
CORPORATE SOURCE: Department of Anatomy with Radiology, University of Auckland, Private Bag 92019, Symonds Street, Auckland, New Zealand.
SOURCE: NEUROSCIENCE, (2000) 100 (4) 677-80.
Journal code: 7605074. ISSN: 0306-4522.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118

ANSWER 18 OF 55 MEDLINE

AB **Huntington**'s disease is a progressive, autosomal dominantly inherited, **neurodegenerative** disease that is characterized by involuntary movements (chorea), cognitive decline and psychiatric manifestations. This is one of a number of late-onset **neurodegenerative** disorders caused by expanded glutamine repeats, with a likely similar biochemical basis. Immunohistochemical studies on **Huntington**'s disease tissue, using antibodies raised to the N-terminal region of huntingtin (adjacent to the repeat) and ubiquitin, have recently identified neuronal inclusions within densely stained neuronal nuclei, peri-nuclear and within dystrophic neuritic processes. However, the functional significance of inclusions is unknown. It has been suggested that the disease-causing mechanism in **Huntington** 's disease (and the other polyglutamine disorders) is the ability of polyglutamine to undergo a conformational change that can lead to the formation of very stable anti-parallel beta-sheets; more specifically, amyloid structures. We examined, using Congo Red staining and both polarizing and confocal microscopy, post mortem human brain tissue from five **Huntington**'s disease cases, two Alzheimer's disease cases and two normal controls. Brains from five transgenic mice (R6/2)(12) expressing exon 1 of the human huntingtin gene with expanded polyglutamine, and five littermate controls, were also examined by the same techniques. We have shown that some inclusions in **Huntington** 's disease brain tissue possess an amyloid-like structure, suggesting parallels with other amyloid-associated diseases such as Alzheimer's and prion diseases.

L4 ANSWER 42 OF 55 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 95083678 MEDLINE
DOCUMENT NUMBER: 95083678 PubMed ID: 7991613
TITLE: Beta-amyloid neurotoxicity requires fibril formation and is inhibited by congo red.
AUTHOR: Lorenzo A; Yankner B A
CORPORATE SOURCE: Department of Neurology, Harvard Medical School, Boston, MA.
CONTRACT NUMBER: AG09229 (NIA)
NS30352 (NINDS)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Dec 6) 91 (25) 12243-7.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199501
ENTRY DATE: Entered STN: 19950124
Last Updated on STN: 19950124
Entered Medline: 19950111

L4 ANSWER 42 OF 55 MEDLINE DUPLICATE 7

AB beta-Amyloid (beta A) is normally produced as a nontoxic soluble peptide. In Alzheimer disease, beta A aggregates and accumulates in the brain as inert diffuse plaques or compact plaques associated with **neurodegenerative** changes. To determine the relationship of neurotoxicity to the physical state of beta A, we created (i) nonamyloidogenic amorphous aggregates of beta A [amorphous beta A (Am-beta A)] analogous to diffuse plaques and (ii) amyloidogenic fibrils of beta A [fibrillar beta A (Fib-beta A)] analogous to compact plaques. In primary rat hippocampal culture, Fib-beta A was neurotoxic, whereas Am-beta A was not toxic. Fib-beta A caused significant loss of synapses in viable neurons, while Am-beta A had no effect on synapse number. The amyloid fibril-binding dye Congo red inhibited Fib-beta A neurotoxicity by inhibiting fibril formation or by binding to preformed fibrils. Congo red also inhibited the pancreatic islet cell toxicity of diabetes-associated amylin, another type of amyloid fibril. These results indicate that beta A neurotoxicity requires fibril formation. These findings and our previous demonstration that amylin fibrils are toxic suggest that a common cytopathic effect of amyloid fibrils may contribute to the pathogenesis of Alzheimer disease and other amyloidoses.

L4 ANSWER 36 OF 55 MEDLINE

ACCESSION NUMBER: 97113673 MEDLINE
DOCUMENT NUMBER: 97113673 PubMed ID: 8955513
TITLE: Beta-amyloid induces apoptosis in human-derived neurotypic SH-SY5Y cells.
AUTHOR: Li Y P; Bushnell A F; Lee C M; Perlmutter L S; Wong S K
CORPORATE SOURCE: Institute for Dementia Research, Bayer Corporation, West Haven, CT 06516, USA.
SOURCE: BRAIN RESEARCH, (1996 Nov 4) 738 (2) 196-204.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970414
Last Updated on STN: 19970414
Entered Medline: 19970403

L4 ANSWER 36 OF 55 MEDLINE

AB Alzheimer's disease is primarily characterized by neurofibrillary tangles, senile plaques, and **neurodegeneration**. The major component of senile plaques is the beta-amyloid peptide (beta A4), which has been shown to be toxic to neurons in vitro. To date, the mechanism of beta A4-induced neurotoxicity has not been determined in human-derived neurons. In this report, we present evidence that programmed cell death, or apoptosis, is involved in the neurotoxic activity of beta A41-40 and beta A425-35 in the human-derived neurotypic cell line SH-SY5Y cells. The evidence for beta A4-induced apoptosis includes: (1) labeling of cell nuclei for DNA nicked ends; (2) morphological changes in ultrastructure that are consistent with apoptosis (shrunken cells with pyknotic nuclei); (3) DNA laddering which can be blocked by aurintricarboxylic acid (ATA), an inhibitor of apoptosis; and (4) marginal release of intracellular lactate dehydrogenase (LDH), an indicator of necrosis. These results suggest that apoptosis is the major event involved in beta A4-induced cytotoxicity in SH-SY5Y cells. A variety of reagents were tested to determine their activities against beta A4-induced DNA laddering. Nerve growth factor and free radical scavengers were inactive in this system. While ATA blocked DNA laddering resulting from either beta A4 or okadaic acid treatment, Congo red specifically attenuated only beta A4-induced DNA fragmentation. These results suggest that compounds which bind fibrillar beta-peptides can protect this human neurotypic cell line against apoptosis induced by beta A4.

L4 ANSWER 35 OF 55 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1996:551309 BIOSIS

DOCUMENT NUMBER: PREV199699273665

TITLE: A model for structure dependent binding of Congo red to Alzheimer B-amyloid fibrils.

AUTHOR(S): Carter, D. B.; Chou, K. C.

CORPORATE SOURCE: CNS Res., Pharmacia and Upjohn Inc., Kalamazoo, MI 49001 USA

SOURCE: Society for Neuroscience Abstracts, (1996) Vol. 22, No. 1-3, pp. 1171.
Meeting Info.: 26th Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 16-21, 1996
ISSN: 0190-5295.

DOCUMENT TYPE: Conference

LANGUAGE: English

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 55 MEDLINE

ACCESSION NUMBER: 1999448183 MEDLINE
DOCUMENT NUMBER: 99448183 PubMed ID: 10516307
TITLE: Protofibrillar intermediates of amyloid beta-protein induce acute electrophysiological changes and progressive neurotoxicity in cortical neurons.
AUTHOR: Hartley D M; Walsh D M; Ye C P; Diehl T; Vasquez S; Vassilev P M; Teplow D B; Selkoe D J
CORPORATE SOURCE: Center for Neurologic Diseases, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: AG00891 (NIA)
AG06173 (NIA)
AG12749 (NIA)
+
SOURCE: JOURNAL OF NEUROSCIENCE, (1999 Oct 15) 19 (20) 8876-84.
Journal code: 8102140. ISSN: 1529-2401.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20010521
Entered Medline: 19991028

L4 ANSWER 26 OF 55 MEDLINE

AB Alzheimer's disease (AD) is a progressive **neurodegenerative** disorder that is thought to be caused in part by the age-related accumulation of amyloid beta-protein (Abeta). The presence of neuritic plaques containing abundant Abeta-derived amyloid fibrils in AD brain tissue supports the concept that fibril accumulation per se underlies neuronal dysfunction in AD. Recent observations have begun to challenge this assumption by suggesting that earlier Abeta assemblies formed during the process of fibrillogenesis may also play a role in AD pathogenesis. Here, we present the novel finding that protofibrils (PF), metastable intermediates in amyloid fibril formation, can alter the electrical activity of neurons and cause neuronal loss. Both low molecular weight Abeta (LMW Abeta) and PF reproducibly induced toxicity in mixed brain cultures in a time- and concentration-dependent manner. No increase in fibril formation during the course of the experiments was observed by either Congo red binding or electron microscopy, suggesting that the neurotoxicity of LMW Abeta and PF cannot be explained by conversion to fibrils. Importantly, protofibrils, but not LMW Abeta, produced a rapid increase in EPSPs, action potentials, and membrane depolarizations. These data suggest that PF have inherent biological activity similar to that of mature fibrils. Our results raise the possibility that the preclinical and early clinical progression of AD is driven in part by the accumulation of specific Abeta assembly intermediates formed during the process of fibrillogenesis.

Entered Medline: 20000830

L4 ANSWER 20 OF 55 MEDLINE
ACCESSION NUMBER: 2000175312 MEDLINE
DOCUMENT NUMBER: 20175312 PubMed ID: 10708675
TITLE: Distribution of beta-amyloid and amyloid precursor protein in the brain of spawning (senescent) salmon: a natural, brain-aging model.
AUTHOR: Maldonado T A; Jones R E; Norris D O
CORPORATE SOURCE: Laboratory of Comparative Reproduction, Department of Environmental, Population and Organismic Biology, University of Colorado, Campus Box 334, Boulder, CO 80309-0334, USA.. maldonad@ucsu.colorado.edu
CONTRACT NUMBER: 1-R03AG15288-01 (NIA)
SOURCE: BRAIN RESEARCH, (2000 Mar 10) 858 (2) 237-51.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000424

L4 ANSWER 20 OF 55 MEDLINE

AB Brain amyloid precursor protein (APP), a normal constituent of neurons, glial cells and cerebrospinal fluid, has several proposed functions (e.g., in neuronal growth and survival). It appears, however, that altered processing of APP is an initial or downstream step in the neuropathology of brain aging, Alzheimer's disease (AD), and Down's syndrome (DS). Some studies suggest that proteolytic cleavage of APP, producing beta-amyloid (Abeta(1-42)), could have neurotoxic or neuroprotective effects. In this study, we utilized antibodies to human APP(695) and Abeta(1-42,) and Congo red staining, to search for amyloid deposition in the brain of semelparous spawning kokanee salmon (Oncorhynchus nerka kennerlyi). Intracellular APP(695) immunoreactivity (APP-ir) was observed in brain regions involved in gustation (glomerulosus complex), olfaction (putative hippocampus, olfactory bulb), vision (optic tectum), the stress response (nucleus preopticus and nucleus lateralis tuberis), reproductive behavior (nucleus preopticus magnocellularis, nucleus preopticus periventricularis, ventral telencephalon), and coordination (cerebellum). Intra- and extra-neuronal Abeta(1-42) immunoreactivity (Abeta-ir) were present in all APP-ir regions except the nucleus lateralis tuberis and Purkinje cells of the cerebellum (coordination). Thus, the relationship between APP and Abeta deposition during brain aging could shed light on the processing of APP into Abeta, **neurodegeneration**, and possible protection of neurons that are functioning in spawning but senescent salmon. Pacific salmon, with their predictable and synchronized life history, could provide research options not available with the existing models for studies of brain aging and amyloidosis.

L4 ANSWER 15 OF 55 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:513905 CAPLUS
DOCUMENT NUMBER: 133:133772
TITLE: Rapid and sensitive detection of aberrant protein(fibril) aggregation in **neurodegenerative** disease diagnosis and drug screening
INVENTOR(S): Bamdad, Cynthia Carol; Bamdad, R. Shoshana
PATENT ASSIGNEE(S): Minerva Biotechnologies Corporation, USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000043791	A2	20000727	WO 2000-US1997	20000125
WO 2000043791	A3	20010726		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2361013	AA	20000727	CA 2000-2361013	20000125
EP 1169646	A2	20020109	EP 2000-913266	20000125
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002540383	T2	20021126	JP 2000-595161	20000125

PRIORITY APPLN. INFO.:
US 1999-117126P P 19990125
US 1999-132288P P 19990503
US 1999-155937P P 19990924
WO 2000-US1997 W 20000125

L4 ANSWER 15 OF 55 CAPLUS COPYRIGHT 2003 ACS

AB Methods, assays, and components are described in which biol. samples can be rapidly and sensitively analyzed for the presence of species assocd. with **neurodegenerative** disease. Techniques and components are provided for diagnosis of disease, as well as for screening of candidate drugs for treatment of **neurodegenerative** disease. The techniques are simple, extremely sensitive, and utilize readily-available components. Binding species, capable of binding a **neurodegenerative** disease aggregate-forming or fibril-forming species, are fastened to surfaces of electrodes and surfaces of particles, or provided free in soln., to bind fibril-forming species and/or be involved in aggregation.

L4 ANSWER 11 OF 55 MEDLINE DUPLICATE 2

AB **Huntington**'s disease (HD) is a late onset **neurodegenerative** disorder caused by a CAG/polyglutamine (polyQ) repeat expansion. PolyQ aggregates can be detected in the nuclei and processes of neurons in HD patients and mouse models prior to the onset of symptoms. The misfolding and aggregation pathway is an important therapeutic target. To better test the efficacy of aggregation inhibitors, we have developed an organotypic slice culture system. We show here that the formation of polyQ aggregates in hippocampal slices established from the R6/2 mouse follows the same prescribed sequence as occurs in vivo. Using this assay, we show that Congo red and chrysamine G can modulate aggregate formation, but show complex dose-response curves. Oral administration of creatine has been shown to delay the onset of all aspects of the phenotype and neuropathology in R6/2 mice. We show here that creatine can similarly inhibit aggregate formation in the slice culture assay.

L4 ANSWER 16 OF 55 MEDLINE DUPLICATE 3

ACCESSION NUMBER: 2000300971 MEDLINE
DOCUMENT NUMBER: 20300971 PubMed ID: 10829068
TITLE: Inhibition of huntingtin fibrillogenesis by specific antibodies and small molecules: implications for **Huntington**'s disease therapy.
AUTHOR: Heiser V; Scherzinger E; Boeddrich A; Nordhoff E; Lurz R; Schugardt N; Lehrach H; Wanker E E
CORPORATE SOURCE: Max-Planck-Institut fur Molekulare Genetik, Ihnestrassee 73, D-14195 Berlin, Germany.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2000 Jun 6) 97 (12) 6739-44. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000720
Last Updated on STN: 20020924
Entered Medline: 20000713

L4 ANSWER 16 OF 55 MEDLINE DUPLICATE 3

AB The accumulation of insoluble protein aggregates in intra and perinuclear inclusions is a hallmark of **Huntington**'s disease (HD) and related glutamine-repeat disorders. A central question is whether protein aggregation plays a direct role in the pathogenesis of these **neurodegenerative** diseases. Here we show by using a filter retardation assay that the mAb 1C2, which specifically recognizes the elongated polyglutamine (polyQ) stretch in huntingtin, and the chemical compounds Congo red, thioflavine S, chrysamine G, and Direct fast yellow inhibit HD exon 1 protein aggregation in a dose-dependent manner. On the other hand, potential inhibitors of amyloid-beta formation such as thioflavine T, gossypol, melatonin, and rifampicin had little or no inhibitory effect on huntingtin aggregation in vitro. The results obtained by the filtration assay were confirmed by electron microscopy, SDS/PAGE, and MS. Furthermore, cell culture studies revealed that the Congo red dye at micromolar concentrations reduced the extent of HD exon 1 aggregation in transiently transfected COS cells. Together, these findings contribute to a better understanding of the mechanism of huntingtin fibrillogenesis in vitro and provide the basis for the development of new huntingtin aggregation inhibitors that may be effective in treating HD.

L4 ANSWER 7 OF 55 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:283993 CAPLUS
DOCUMENT NUMBER: 134:307615
TITLE: Method of altering protein aggregation and therapeutic uses
INVENTOR(S): Villegas, Virtudes; Zurdo, Jesus; Aviles, Francesc; Dobson, Christopher Martin; Serrano, Luis
PATENT ASSIGNEE(S): Isis Innovation Limited, UK
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001027152	A1	20010419	WO 2000-GB3974	20001016
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1222203	A1	20020717	EP 2000-968122	20001016
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003512029	T2	20030402	JP 2001-530370	20001016

PRIORITY APPLN. INFO.: GB 1999-24484 A 19991015
WO 2000-GB3974 W 20001016
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 55 CAPLUS COPYRIGHT 2003 ACS

AB The present invention provides a method of designing a modified polypeptide having an altered tendency to aggregate compared to the unmodified polypeptide. The method comprises: analyzing the amino acid sequence of a predetd. polypeptide to det. the propensity of the polypeptide to form local structure; comparing the propensity to form local structure of a modified polypeptide to the propensity to form local structure of an unmodified polypeptide; and detg. thereby whether the modified polypeptide has an altered tendency to aggregate in the denatured state relative to the unmodified polypeptide. A selected modified polypeptide having the altered tendency to aggregate is then produced. The invention also provides a method of producing a modified polypeptide having an altered tendency to aggregate compared to the unmodified polypeptide, which method comprises: (i) introducing at least one amino acid modification into a predetd. polypeptide sequence such that said modified polypeptide has an altered propensity to form local structure in the denatured state relative to the unmodified polypeptide, and optionally (ii) recovering the modified polypeptide, and/or optionally (iii) allowing the modified polypeptides to form an aggregate. Use of the method of altering protein aggregation in a method of treatment or diagnosis of an amyloid or aggregate assocd. disease is disclosed.